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Outcomes of ADHD symptoms in late adolescence: Are developmental subtypes important?

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Abstract

Objective: Substantial individual variation exists in the age of onset and course of ADHD symptoms over development. We evaluated whether, within this variation, meaningful developmental subtypes can be defined.

Method: Using growth mixture modelling in a community-based sample (n=1571), we analysed ADHD symptom trajectories based on measures taken at ages 7,8,9,10,11,13 and 15. We evaluated whether those showing developmental trajectories characterised by later onsets versus early onsets differed in terms of mental health and behavioural outcomes in late adolescence (age 17).

Result: The late onset category was best conceptualised as a milder subtype than early onset. The former was, however, more similar in outcomes to the latter than to the unaffected category, suggesting that later onsets are still associated with impairment.

Conclusion: Considering diagnoses for those affected by ADHD symptoms but who don't meet current age of onset criteria may be important for ensuring that they receive appropriate support.

Keywords: ADHD, subtypes, development

Attention deficit hyperactivity disorder (ADHD) is defined by impairing levels of inattention and/or hyperactivity/impulsivity (American Psychiatric Association [APA], 2013). ADHD symptoms are associated with a range of adverse outcomes, including increased substance use, gambling and other risky behaviour; school, social and occupational difficulties; criminality and antisocial behaviour; and mental health problems (Humphreys & Lee, 2011; Lin, Yang, & Gau, 2015; Mannuzza, Klein, & Moulton, 2008; Murray, Eisner, Obsuth & Ribeaud, 2017; Tai, Gau, Gau, & Chiu, 2013). Among those affected by ADHD symptoms, however, there is considerable variation in symptom trajectories over development. Organising this heterogeneity into clinically useful subtypes can aid diagnosis and treatment. Establishing whether developmental subtypes differ with respect to the various outcomes associated with ADHD symptoms can, for example, provide information on whether different symptom trajectories indicate different types or intensities of support needs and inform individualised treatment approaches. In this study we, therefore, evaluated whether there are developmental subtypes of inattention and hyperactivity/impulsivity symptoms that differ in their late adolescent outcomes.

Though traditionally conceptualised as a childhood disorder with an early onset, it is increasingly being recognised that there is considerable variation in ADHD symptom trajectories over the life course (e.g. Lin, Lo, Yang, & Gau, 2015). Recently, in response to the evidence that age of onset is frequently after early childhood for those who meet diagnostic criteria for ADHD, clinical diagnostic criteria were amended from onset before age 7 in DSM-IV (APA, 1993) to onset before age 12 in DSM-5 (APA, 2013). In fact, some studies indicate that, for a substantial proportion of adults with ADHD symptoms, onset does not occur until as late as adulthood (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015). This has led to calls for further raising the cut-off for the age of onset criterion (Chandra, Biederman, & Faraone, 2016).

Whether variations in age of onset are informative about differences in etiology and outcomes of ADHD symptoms, however, remains somewhat unclear. Evidence from clinical samples have mostly focussed on the extent to which the adolescent and adulthood correlates of early versus ‘late onset’ ADHD differ (Faraone et al., 2006; Faraone, Kunwar, Adamson, & Biederman, 2009; Karam et al., 2009; Lin et al., 2015). Defining late versus early onset in accordance with DSM-IV criteria where ‘late onset’ means after age 7, Faraone et al. (2006) found that those with late versus early onset ADHD scored similarly on a range of neuropsychological tests. Based on this same definition; however, Karam et al. (2009) identified several differences between those with a late versus early onset of ADHD. They found that those with a ‘late onset’ had fewer problems with authority and discipline, less severe symptoms, but higher levels of comorbid anxiety disorders. The extent of comorbidity with other major psychiatric disorders was similar. On the other hand, Guimaraes-da-Silva et al. (2012) found no differences in cognitive and attention features, but higher scores on novelty seeking in the early onset group. Analyses reported by Chandra et al. (2016) suggested that the same mixed picture holds true when late and early onset are defined with respect to DSM-5 criteria. They found that, when measured in adulthood, those with an onset of ADHD symptoms before versus after age 12 had similar patterns of comorbid psychiatric disorders, similar functional impairments and similar levels of intellectual ability. However, the ‘late onset’ group had fewer inattention and hyperactive-impulsivity symptoms but poorer social functioning and quality of life.

There are, however, several limitations of clinical sample studies that could serve to mask or reduce the power to detect differences between developmental subtypes. First, by creating distinct categories of late versus early onset (as per diagnostic criteria), these studies do not model the full variation that exists in age of onset. Second, by relying on retrospective recall of age of onset group, the reliability of the classification of late versus early onset is

likely to be suboptimal. Third, using clinically ascertained samples introduces restriction of range of ADHD symptoms (e.g. Murray, McKenzie, Kuenssberg, & O'Donnell, 2014).

Further, clinically ascertained samples tend to be subject to certain biases that make them non-representative of the underlying population of individuals with ADHD symptoms. For example, those with comorbid conditions or more 'externalising' profiles may be more likely to present at clinical services because these individuals may have a higher overall or more obvious impairment. Similarly, more externalising profiles, irrespective of ADHD symptom severity, are more likely to be associated with earlier detection, thus introducing further potential error into retrospectively recalled ages of onset.

Growth mixture modelling studies in community samples have complementary strengths and weaknesses as compared to clinical sample studies. While they do not rely on (at least somewhat arbitrary) categorisations of late versus early onset, on selected samples or on retrospective recall of age of onset, they tend to lack comprehensive clinical assessments for ADHD symptoms. Growth mixture analyses in community samples have supported the notion that there is considerable heterogeneity in when and how ADHD symptoms develop (Arnold et al., 2014; Malone, Van Eck, Flory, & Lamis, 2010; Murray, Obsuth, Eisner & Ribeaud, 2017a; Pingault, Vitaro, Genolini, Falissard, & Côté, 2011; Robbers et al., 2011). This technique can be used to summarise developmental trajectories in terms of a small number of categories. These studies have shown that in the general population, the majority of individuals tend to show consistently low levels of ADHD symptoms; however, those that show elevated symptom levels may follow a range of different trajectories.

In a growth mixture analysis of a community sample of individuals followed from school entry age to adolescence, for example, Robbers et al. (2011) found that those showing elevated levels of inattention problems at any stage of development could be characterised by one of two developmental trajectories: Approximately 15% of their total sample followed an

initially low but increasing trajectory (i.e. worsening symptoms over time) , while about 20% of their total sample followed an initially high but decreasing trajectory (improving symptoms over time).

Using a similar approach and sample, Pingault et al. (2011) found that inattention and hyperactivity trajectories among those affected by elevated symptoms could be characterised as ‘rising’ (prevalence for inattention/hyperactivity = 18%/14%), ‘declining’ (prevalence for inattention/hyperactivity = 19%/16%) or (stably) ‘high’ (prevalence for inattention/hyperactivity = 17%/10%) trajectory over the same developmental period. That is, among those affected by elevated symptoms at some stage of development, symptoms could either improve, worsen or remain persistently high across the developmental period studied.

Using the same technique in a community sample with data spanning the period from 7 to 19, Döpfner et al. (2015) found that levels of ADHD symptoms varied across developmental trajectory groups, but all showed declines over time. In a previous study in the current sample (spanning ages 7 to 15; Murray et al., 2017b), four developmental trajectories overall were identified for both inattention and hyperactivity/impulsivity: ‘low but increasing’, ‘high but decreasing’, ‘low stable’ and ‘high stable’. For inattention, the proportions of the sample falling into these respective categories were 7%, 10%, 63% and 20%. The corresponding proportions for hyperactivity/impulsivity were 5%, 13%, 73% and 8%.

Few studies in the growth mixture tradition have examined the patterns of impairment of the different developmental subtypes identified. In a previous study with the current sample Murray, Obsuth et al., (2017), evaluated predictors of developmental trajectory group (based on ADHD symptoms measured from age 7 to 15 in approximately yearly intervals). The study found that anxiety and reactive aggression at age 7 were associated with greater likelihood of being a member of the ‘high stable’ group than the ‘initially low but increasing’

class. They also found that the ‘initially low but increasing’ group differed significantly from the ‘low stable’ group on sensation-seeking but still evidenced overall lower levels of sensation-seeking than the ‘high stable’ group. This led the authors to speculate that the ‘low but increasing’ class may represent a milder subtype that evidences impairment primarily in the ‘bottom-up’ executive processes outlined in the dual pathway model of ADHD (Sonuga-Barke, 2003; Young, Heptinstall, Sonuga-Barke, Chadwick, & Taylor, 2005). This study did not, however, look at outcomes of ADHD developmental subtypes. Another study found that ADHD symptom trajectory shape across grades 3 to 9 predicted substance use (Malone et al., 2010). Specifically, substance use onset was earlier in those with symptoms that were initially higher but declined towards early adolescence as compared to those with symptoms that rose to a peak in adolescence and declined thereafter. Finally, Pingault et al. (2011) found that a higher proportion of individuals with ‘rising’ inattention symptom trajectories had graduated from high school compared to individuals with (stably) ‘high’ trajectories.

Overall, the evidence hints at some differences between developmental subtypes, especially for individuals who have symptom trajectories characterised by earlier versus later onset. Some studies suggest the latter may represent a milder form of ADHD while others hint at possible qualitative distinctions between individuals with different ages of onset. In this study, we aimed to build on this preliminary evidence to evaluate developmental subtype differences in a broader range of candidate ADHD outcomes. We evaluated potential differences between developmental subtypes in internalising symptomology, reactive and proactive aggression, delinquency, prosociality, and substance use, all of which have been previously linked to ADHD (Kofler, Larsen, Sarver, & Tolan, 2015; Molina & Pelham, 2014; Murray, Obsuth, Zirk-Sadowski, Ribeaud, & Eisner, 2016). We also investigated violent ideations: thoughts, fantasies or daydreams of harming another person. These are associated with mental health dimensions, aggression, victimisation self-control and other constructs

associated with ADHD symptoms (Murray, Eisner, & Ribeaud, 2016; Murray, Obsuth, Eisner, & Ribeaud 2017b). Violent ideations have not previously been extensively explored in relation to ADHD but we hypothesise that they can be an outcome of the difficulties in controlling cognitions and that are associated with ADHD. Finally, we investigated differences in self-reported ADHD symptoms in late adolescence.

Method

Participants

Participants were from the Zurich Project on Social Development from Childhood to Adulthood (z-proso). Z-proso is a longitudinal cohort study of anti-social and pro-social behavioural development. The current sample includes $n = 1571$ (761 female, 810 male) z-proso participants with teacher-reported ADHD symptom data available for at least one measurement wave. This represents 94% of the baseline target sample which was determined based on school-level stratified random sampling. All children entering the first grade (aged ~7) of 56 selected schools were invited to participate.

Children participated in eight main measurement waves. Measurement waves are labelled according to these ages rounded down to the nearest whole number. The median age and number of participants were: 7.45 ($n = 1338$), 8.23 ($n = 1314$), 9.21 ($n = 1287$), 10.70 ($n = 1262$), 11.60 ($n = 1061$), 12.63 ($n = 972$), 13.88 ($n = 1239$), and 15.68 ($n = 1267$). Parental written consent to participate was obtained for the first six years of the study. Parents were offered a financial incentive equivalent to approximately 30 USD. When participants reached age 13, the consent procedure changed such that participants themselves then gave their active consent to participate and parents received an information letter that allowed them to opt out their child. At age 13, participants were offered a financial incentive worth approximately 30 USD and at age 15 they were offered a financial incentive worth

approximately 50 USD. Further information on the z-proso project can be found on the study website: <http://www.cru.ethz.ch/en/projects/z-proso.html>.

Measures

ADHD symptoms across development versus outcomes in adolescence were measured by different raters. This is advantageous because it avoids inflated associations due to common rater bias. ADHD symptoms were measured using teacher reports in a questionnaire administered in paper and pencil format. This was embedded in a larger questionnaire that measured other aspects of youth behaviour. Internalising, prosociality, aggression, violent ideations, substance use and ADHD symptoms at age 17 were all measured via self-reports. All self-report measures were administered in German (the official language of the study location) in paper and pencil format. They were embedded in a larger questionnaire which also included questions about attitudes, experiences, risk factors and outcomes related to prosocial and antisocial behaviour.

Inattention and Hyperactivity/Impulsivity

ADHD symptoms across development were measured using an adapted version of the *Social Behavior Questionnaire* (SBQ; Tremblay et al., 1991). Four items refer to inattention and four items refer to hyperactivity/impulsivity symptoms. Item contents in English are provided in Supplementary Materials. Item responses were provided on a five point Likert scale from *Never* to *Very Often*. The reliability and validity of the teacher-reported SBQ has been supported in previous research, including in the current sample (e.g. Murray, Eisner, & Ribeaud, 2017; Tremblay et al., 1991). The overall reliabilities for these scales at ages 7 to 15 as estimated by Cronbach's range from .95 to .96 for inattention and from .92 to .93 for hyperactivity/impulsivity. In this study, we used factor scores for inattention and hyperactivity/impulsivity estimated from a longitudinal factor model where at each wave

ADHD was specified as a first-order oblique factor model with correlated inattention and hyperactivity/impulsivity factors. The mean and variance of the attention deficit and hyperactivity/impulsivity factors at age 7 were fixed to 0 and 1 respectively and the intercept and loading of the first item of each first-order factor equal across time for scaling and identification. Residual covariances between the same items at different waves were freely estimated. The model was estimated using maximum likelihood estimation in *Mplus 7.31* (Muthén & Muthén, 2015). Factor score determinacies were all >0.90 .

For the majority of children, the same teacher taught and provided ratings between grades one and three; i.e. at ages 7, 8, and 9. They then had another teacher between grades four to six; i.e. at ages 10, 11, and 12 before transitioning to secondary school for the data collection waves at ages 13 and 15. For the first three waves of data collection, teachers were not compensated for their participation. For all subsequent data collection waves teachers with at least seven participants in their class received a book voucher worth approximately 50 USD. The numbers of teachers providing ratings at the measurement waves included in this study were: 113, 148, 217, 274, 265, 258, 366, and 423, respectively.

Internalising, prosociality, aggression, violent ideations and ADHD symptoms

Internalising, prosociality aggression and ADHD symptoms at age 17 were measured using an adapted version of the Social Behavior Questionnaire (SBQ; Tremblay et al., 1991). Violent ideations were measured using the *Violent Ideations Scale (VIS)*; Murray, Eisner & Ribeaud, 2016). All items are measured on a 5-point Likert scale from *never* to *very often*.

The psychometric properties of the self-reported SBQ was investigated in Murray, Obsuth, Eisner, and Ribeaud (2017c) and Murray, Eisner & Ribeaud (2017). In a longitudinal invariance analysis, Murray, Obsuth, Eisner & Ribeaud (2017c) found that the internalising, aggression and ADHD items showed at least metric invariance over the developmental period

covering ages 11 to 17. Murray et al. (2017b) provided evidence for the factorial validity of the SBQ and VIS, finding that in a joint exploratory factor analysis of the self-reported SBQ items and the VIS as administered to the current sample at age 17, the vast majority of items loaded on the intended factors. This provides support for the factorial validity of the SBQ and VIS.

In this study, we used factor scores derived from confirmatory factor analysis (CFA) models for each dimension. These models were based on past exploratory and confirmatory factor analyses in the sample (Murray et al., 2017b). Dimensions were: Internalising, Prosociality, Reactive/Physical Aggression, Proactive/Indirect Aggression and Violent Ideations. These were estimated in *Mplus 7.31* using weighted least squares means and variances (WLSMV). This method does not allow for the estimation of factor score determinacies; therefore, we also fit the models using maximum likelihood estimation to check that factor score determinacies were likely to be adequate. All factor scores had determinacies >.90 except those for ADHD, which were slightly below this at .88.

Substance Use

Substance use items were preceded by the instruction ‘Listed below are some drugs, intoxicants and other substances. Have you ever taken any of them and if yes, how many times in the last 12 months (i.e. since [DATE])?’ Participants then indicated tobacco, alcohol (beer/alcopops) and alcohol (spirits) use over the previous 12 months. Each was measured with a single item, with responses recorded on a 6-point scale from *never* to *daily*, specifically: (‘never’, ‘once’, ‘2 to 5 times’, ‘6 to 12-times (monthly)’, ‘13 to 52 times (weekly)’ and ‘53 to 365 times (daily)’).

Delinquency

Delinquency was measured as the sum of 5 items measuring truancy, cheating at school, running away from home, illegal upload/download and fare dodging. The scale is an adaptation of the scale used for a large comparative survey among German cities carried out by the Criminological Research Institute of Lower Saxony (KFN) (Wetzels, Enzmann, Mecklenburg, & Pfeiffer, 2001), which in turn is based on a scale developed by Lösel (1975). Items were scored dichotomously with participants indicating ‘yes or ‘no’ regarding whether they had engaged in the specified acts of delinquency over the previous 12 months.

Statistical Procedure

Growth mixture models

We used growth mixture models (GMM) to model heterogeneity in ADHD symptom trajectories (e.g. Nylund, Bellmore, Nishina, & Graham, 2007). GMM assumes that individuals belong to categories defined by similar developmental trajectories that can collectively be captured by a latent categorical variable. The number of classes that this latent categorical variable has is usually not known a priori, but determined from the data based on statistical tests, information theoretic comparisons and informed by substantive theory. The lo-mendall-rubin (LMR) provides an approximation to a likelihood ratio test for latent class analyses (where the traditional likelihood ratio test cannot be applied in a straightforward manner due to the involvement of parameters constrained to the boundary of parameter space). When the p -value associated with the LMR test is $<.05$, a model with $k-1$ classes can be rejected in favour of a model with k classes. When the LMR gives ambiguous results and/or to provide an additional information source, information theoretic criteria such as AIC, BIC and saBIC can also be compared across models differing in their number of classes. Smaller (more negative) values indicate better fitting models.

We utilised optimal growth mixture model solutions developed in a previous study in the same sample based on the above-described method. We did this separately for inattention and hyperactivity/impulsivity because of previous evidence that they can have different developmental trajectories (Arnold et al., 2014). Methods are comprehensively described in Murray et al. (2017b). In brief, the study compared model fits and examined model parameters for a range of models with different numbers of latent classes (from 1 to 6). The models were fit to factor scores derived from longitudinal measurement models where ADHD was specified as an oblique model with inattention and hyperactivity/impulsivity specific factors. The measurement model was estimated in *Mplus 7.31* (Muthén & Muthén, 2014) and yielded factor score determinacies for inattention and hyperactivity/impulsivity >0.90. Most of the youth were rated by the same teacher across the first three waves and the last three waves. In the latent growth curve models we, therefore, also included residual covariances between inattention (or hyperactivity/impulsivity) factor scores across waves 1 to 3 and across waves 4 to 6. We found that, on balance, 4-class solutions with a linear slope factors only (i.e. no higher order growth) were optimal for both inattention and hyperactivity/impulsivity. The resulting trajectory classes were similar for inattention and hyperactivity/impulsivity. The four trajectories are summarised in Figures 1 and 2 and Tables 3 and 4 and can be characterised as ‘late onset’, ‘persistent’, ‘unaffected’ and ‘remitting’. Entropy for the inattention model was .75 while entropy for the hyperactivity/impulsivity model was .87. There was a statistically significant association between class membership for the inattention phenotype and for the hyperactivity/impulsivity phenotype ($p < .001$) with those in an affected-at-adolescence group for one phenotype (‘late onset’ or ‘persistent’) tending to be in an affected-at-adolescence group for the other. The exception was that those in the ‘remitting’ group for hyperactivity/impulsivity were slightly more likely to be in the early onset/‘persistent’ than the corresponding ‘remitting’ group for inattention.

In this study, we also repeated the above procedure with gender as a predictor of the latent categorical class membership variable given the evidence for differences in symptom levels, profiles and developmental trajectories (e.g. Williamson & Johnston, 2015). In this method, the classes formed were conditional on gender.

Predicting late adolescent outcomes

At first, individual models were fit for each late adolescent outcome using the three-step approach outlined in Asparouhov and Muthén (2014). In brief, the method involves first estimating the latent class model absent any distal outcomes i.e. using only the latent class indicators which in this case are the variables recording inattention and hyperactivity/impulsivity. From this model, classification uncertainty is computed using the latent class posterior distribution. Finally, the most likely class variable from the model estimated in the first step is used to predict a distal outcome variable, using the classification uncertainty rates to correct for latent class measurement error. This is achieved through fixing the relation between the latent class variable and the observed most likely class variable. The procedure is conceptually similar to correcting a correlation coefficient for unreliability. Developmental subtype differences in outcomes are evaluated using a Wald test. For this we assumed unequal within-class outcome variances. We repeated the above-described analyses controlling for gender by using the classes formed with gender as a covariate.

Results

Growth Mixture Models

Unconditional growth mixture models were derived from previous research and are described in the Method section. Model fits for the inattention and hyperactivity/impulsivity growth mixture models conditional on gender are provided in Tables 1 and 2 in Supplementary Materials. Based on the LMR test for the linear growth models for

inattention, a 5-class solution was preferred. The same test applied to the models with both linear and quadratic growth suggested that a 3-class solution was to be preferred; however, this was based on an only marginally non-significant LMR test ($p = 0.055$), therefore, a 4-class solution was also considered. Of the three models, the 4-class linear and quadratic growth model had the lowest BIC, AIC and saBIC followed by the 5-class linear growth model. Between these two models, the 5-class linear model was preferred on balance because the inclusion of both linear and quadratic growth yielded estimation problems such as out of range parameter estimates. As these can be indicative of over-parameterisation we preferred the more parsimonious 5-class linear model instead. This model is summarised in Figure 3 and Table 1. The 5 classes could be characterised as ‘persistent’, ‘remitting’, ‘late onset’, ‘unaffected’ and ‘mild’.

Based on the LMR test for the linear growth models for hyperactivity/impulsivity, a 4-class solution was supported. The same test applied to the models with linear and quadratic growth supported a 2-class model. Of these two models the linear 4-class model fit better according to AIC, BIC and saBIC and was thus judged the optimal class solution overall. This model is summarised in Figure 4 and Table 1. The 4 classes could be characterised as ‘persistent’, ‘remitting’, ‘unaffected’ and ‘late onset’. These classes were similar to those derived absent gender as a covariate.

Outcomes of class membership

Results of the univariate models in which trajectory class predicts a series of late adolescence outcomes are provided in Tables 2 and 3. These tables provide results using both the unconditional GMMs and controlling for gender by using the GMMs with classes formed conditional on gender. We focus on three comparisons: ‘late onset’ versus ‘persistent’; ‘late onset’ versus unaffected; and ‘persistent’ versus ‘unaffected’. The ‘late

onset' versus 'persistent' group comparison provides information about variations in outcomes depending on when elevated symptom levels first manifest. The 'late onset' versus 'unaffected' group comparison provides information about whether the 'late onset' group is impaired relative to those who never show elevated levels of ADHD symptoms. The 'persistent' versus 'unaffected' group comparison provides a check that individuals with early onset and persistently elevated symptoms show the expected impairments relative to 'unaffected' individuals.

Based on the unconditional growth mixture models for inattention, the 'late onset' group evidenced higher levels of reactive/physical aggression, violent ideations, delinquency and cigarette smoking than the 'unaffected' group. The 'persistent' and 'late onset' groups differed only in reactive aggression with the latter showing significantly lower levels. There were no differences between the groups in self-reported ADHD symptoms at age 17.

For the growth mixture models conditional on gender, all but one of the late adolescent outcome variables (self-reported ADHD at age 17) affected the formation of the latent classes when regressed on the latent categorical variable for trajectory membership. This is indicated by a more than 20% change in class membership with the addition of the distal outcome. We, therefore, analysed these data using the BCH method described by Bakk and Vermunt (2016). Its implementation in Mplus is comprehensively described by Asparouhov and Muthén (2014). In brief, the BCH is similar to the 3-step method but its final stage is a multi-group model to evaluate class differences by outcome. In this model, observations are weighted to reflect measurement error in the latent class variable based on a latent class measurement model estimated absent the distal outcome. In using a multi-group model in the last stage, the method does not allow class formation to be affected by the inclusion of a distal outcome. Based on the growth mixture models conditional on gender for inattention, the 'late onset' group showed significantly higher levels of proactive aggression,

reactive aggression, violent ideations, delinquency and cigarette use than the ‘unaffected’ group. The ‘late onset’ group also showed significantly lower levels of internalising than the ‘unaffected’ group. The ‘late onset’ group did not differ significantly from the ‘persistent’ group on any of the adolescent outcomes evaluated. The ‘persistent’ group showed significantly higher levels of proactive aggression, reactive aggression, violent ideations, delinquency, cigarette smoking and spirit consumption than the ‘unaffected’ group. The ‘persistent’ group also showed significantly lower levels of prosociality and internalising than the ‘unaffected’ group.

Based on the unconditional growth mixture models for hyperactivity/impulsivity, the ‘late onset’ group evidenced significantly higher levels of proactive aggression, violent ideations, delinquency and cigarette smoking than the ‘unaffected’ group. The ‘late onset’ group also showed significantly lower levels of internalising than the ‘unaffected’ group. The ‘persistent’ and ‘late onset’ groups differed significantly in terms of reactive aggression, again with the latter group showing lower levels. The ‘persistent’ group differed significantly from the unaffected group on all outcomes except prosociality and alcohol use.

Based on the growth mixture models for hyperactivity/impulsivity conditional on gender, the late onset group differed significantly from the ‘unaffected’ group on internalising, reactive aggression, violent ideations, delinquency and cigarette smoking. In all cases, except internalising, it was the ‘late onset’ group that scored higher. The ‘late onset’ group differed from the ‘persistent’ group only on reactive aggression, with the ‘persistent’ group showing higher levels. The ‘persistent’ group differed significantly from the ‘unaffected’ group on all outcomes except prosociality and alcohol use.

Discussion

In this study, we evaluated whether developmental subtypes of ADHD differ in late adolescent outcomes associated with ADHD. Developmental subtypes were operationalised using growth mixture models of symptom trajectories over ages 7 to 15. In particular, we evaluated whether those with higher levels of ADHD symptoms in adolescence differed depending on whether high levels were evident from childhood and persisted or rose over development. Overall, the evidence suggested that this latter category (henceforth ‘late onset’) represented a milder developmental subtype than the ‘early onset/persistent’ type.

We analysed inattention and hyperactivity/impulsivity symptoms separately because of past evidence suggesting dissociable developmental trajectories for these two symptom domains (e.g. Arnold et al., 2014). Indeed, in the current study, there were some differences between inattention and hyperactivity/impulsivity in terms of the developmental subtypes identified and their relations to adolescent outcomes. For example, an additional subtype was supported for inattention reflecting a differentiation of those with low symptoms levels across development into an ‘unaffected’ and ‘mild’ class. In addition, after controlling for gender, while the ‘late onset’ and ‘persistent’ hyperactivity/impulsivity classes differed on reactive aggression, there were no significant differences in adolescent outcomes between the analogous categories for inattention. However, the broader pattern of results as regards associations between developmental subtype and late adolescent outcomes was similar across the domains. For both domains, the early onset/‘persistent’ and ‘late onset’ subtypes evidenced poorer outcomes for a range of variables as compared to those who could be classified as ‘unaffected’. This is in line with the idea that those with later ages of onset of ADHD symptoms still experience worse outcomes than those with stably low levels of symptoms. Evidence that profiles of impairment do not differ according to age of onset has been cited as evidence in favour of raising the age of onset criterion from 7 to 12 years; the

logic being that those with a later age of onset are no less in need of clinical intervention (Faraone et al., 2009).

We did, however, find some evidence that the ‘early onset’/‘persistent’ subtypes represented the more severe phenotype in terms of their early adolescent outcomes. For example, the hyperactivity/impulsivity ‘persistent’ group showed significantly higher levels of reactive aggression than the hyperactivity/impulsivity ‘late onset’ group. In addition, the ‘persistent’ groups tended to a larger number of significant differences to the ‘unaffected’ groups. Thus, although the later onset group were generally more similar to the early onset group than the ‘unaffected’ group, the latter represented an overall milder developmental subtype.

There are several possible explanations for the differences in late adolescent outcomes observed between the ‘late onset’ and ‘persistent’ categories of ADHD identified in the current study. It is possible that earlier ADHD symptom onset indexes greater severity of underlying impairments, with this greater severity also reflected in poorer late adolescent outcomes. Our results provide mixed evidence on this. In the growth trajectory models conditional on gender, the ‘persistent’ groups showed symptom levels higher than those of the ‘late onset’ groups by the end of the studied period. Thus, the teacher reports support the idea that ADHD symptom severity is greater for those with an earlier onset. However, self-reported ADHD symptoms differed between the ‘late onset’ and ‘persistent’ groups at age 17 only for the hyperactivity/impulsivity subtypes (not inattention). In general, the developmental subtypes could not be clearly differentiated on the basis of age 17 self-reported symptoms. This may reflect weaknesses in our self-report measure which comprised only 4 items. However, the reliability of self-reports for ADHD has been questioned in general (e.g. Faraone & Biederman, 2016). For example, in a previous similarly-aged sample (mean age = 20.2 years), those without ADHD symptoms in childhood tended to over-report

current ADHD symptoms, while those who had ADHD symptoms in childhood tended to under-report current ADHD symptoms (e.g. Sibley et al., 2012).

Another possible explanation is that individuals with a later onset may have the same underlying degree of ADHD characteristics but may, for example, have compensatory supports in the school or family. For these individuals, symptoms may not become manifest until they gain independence and are able to rely on such supports to a lesser extent. Compensatory or protective factors could also be individual characteristics such as higher cognitive ability. Faraone and Biederman (2016) offered this diminishing ‘compensatory’ supports explanation for adult onset ADHD; however, it can equally be applied to variations in age of onset more generally. These early protective factors may not ultimately prevent ADHD symptom expression, but they may attenuate its impact over development.

Another possibility is that those with an earlier onset have worse outcomes because they accumulate adverse experiences over a longer time period. For example, individuals with ADHD symptoms are more likely to have difficulties in the social and academic domain and to affiliate with more deviant peers (e.g. Bennet et al., 2004; Hoza, 2007). These experiences could promote outcomes such as reactive aggression.

There may also be certain critical periods in which ADHD symptoms create the greatest risk of adverse outcomes. For example, it has been proposed that early ADHD onsets can contribute to setting individuals on a lifelong trajectory characterised by escalating behaviour problems which become ingrained from early life through, for example, coercive cycles of interaction with parents, selection of more deviant peer groups, poor relationships with teachers, the selection of criminogenic environments and early onset of substance use (e.g. Beauchaine & McNulty, 2014). On the other hand, onset of symptoms after the early childhood and early school period may mean that this critical risk window is missed. In

addition, an absence of symptoms up to this point may allow individuals to accumulate protective factors such as positive peer, parent and teacher relationships and overall greater social support that can mitigate impact after symptom onset.

Finally, those with later and earlier onsets may have distinct etiologies. For example, early onsets could to a greater extent reflect inherited traits while later onsets reflect, for example, subtle acquired brain damage in regions underpinning executive functions. Murray et al. (2017a), for example, proposed that substance use in adolescence could affect the vulnerable and still-maturing prefrontal cortices that play an important role in ADHD-like behaviours. They found no evidence for this hypothesis; however, other exposures are yet to be explored. Later onsets could also reflect impairments that are especially sensitive to hormonal activation effects at puberty (e.g. see Martel, Klump, Nigg, Breedlove, & Sisk, 2009). Given the fledging status of this area of research, there remains considerable work to be done in disentangling these various possibilities for why individuals with ADHD symptoms follow variable developmental trajectories.

It is interesting to note the similarity of our results to those found in relation to developmental subtypes observed for the conduct problems which are highly comorbid with and often preceded by ADHD (Angold, Costello, & Erkanli, 1999; Nock, Kazdin, Hiripi, & Kessler, 2007). Here, a large number of studies have suggested that, among those with conduct problems in adolescence and beyond, those with an adolescent onset have fewer brain abnormalities, a lower loading of risk factors and fewer adverse outcomes than those with a childhood onset (e.g. Fairchild, Goosen, Calder, & Goodyer, 2013). As such, the general idea that adolescent onset conduct problems can be considered a milder developmental subtype than childhood onset conduct problems has been supported. This raises the possibility that ADHD developmental subtypes could not just mirror but partly underpin those identified with respect to conduct problems. Indeed, using a parallel process

modelling approach, Murray et al. (2016a) found that ADHD symptom trajectories covaried strongly with aggression developmental trajectories. Similarly, using a growth mixture approach, van Lier, Der Ende, Koot, and Verhulst (2007) demonstrated that oppositional defiant disorder and conduct disorder (CD) developmental trajectory class membership was associated with an ADHD trajectory class membership. In their study, all individuals who showed an ADHD developmental trajectory characterised by high symptom levels were also in conduct problem trajectory classes characterised either by an adolescent peak or moderate conduct problem levels; none were in a conduct problems class characterised by low symptom levels. Similar results were reported by Howard et al. (2015) in a clinical ADHD sample who found that individuals who followed a particular trajectory of ADHD symptoms (e.g. worsening versus improving) tended to be assigned to the analogous category for delinquency. These studies are correlational and therefore cannot be used to determine whether ADHD subtypes underpin CD subtypes; CD subtypes underpin ADHD subtypes; or some third phenotypic subtypes (e.g. oppositional defiant disorder; ODD) underpins both. However, independent evidence has suggested that ADHD has an earlier age of onset than both ODD and CD (e.g. Nock et al., 2007). Moreover, ADHD predicts later conduct problems whereas conduct problems do not seem to predict future ADHD (e.g. Burke, Pardini, & Loeber, 2008; Nock et al., 2007). This would be most consistent with ADHD acting as a fundamental underlying phenotype responsible for commonalities across CD and ADHD developmental subtypes.

Limitations

One limitation of the current research is reliance on a single rater of age 7 to 15 ADHD symptoms, namely teachers. One possibility is that the later versus earlier onset group differences in severity partly reflected those with greater overall levels of difficulty-irrespective of diagnostic domain- being more visible to the teachers who rated ADHD

symptoms. This could make it more likely for teachers to identify their ADHD symptoms early on as compared to those with similar ADHD symptoms but with fewer additional difficulties. However, to avoid inflation of associations between developmental subtypes and late adolescent outcomes due to common rater biases, we used self-reports to assess adolescent outcomes. Finally, our measure of ADHD symptoms was brief and it will be important to replicate the findings of the current study using a more comprehensive and extensively validated measure.

Conclusions

Developmental subtypes differing in patterns of symptom development from childhood to adolescence can be distinguished. The developmental subtypes characterised by a later onset of symptoms appears to represent an overall milder subtype of ADHD in terms of its outcomes than the developmental subtype with persistently high levels of symptoms from childhood. However, those with a later onset still evidenced worse outcomes in late adolescence than ‘unaffected’ individuals. As such, our results support the idea that ADHD diagnoses should be considered irrespective of age of onset.

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Table 1

Key parameters from growth mixture models

| Class | Prevalence* | Intercept Mean | Linear Slope Mean | Intercept-Linear slope covariance |
|--|--------------------|-----------------------|--------------------------|--|
| Inattention unconditional | | | | |
| 1- unaffected | .63 | -0.48 | -0.05 | -0.09 |
| 2- remitting | .10 | 1.19 | -1.49 | -0.09 |
| 3- persistent | .20 | 0.82 | 0.07 | -0.09 |
| 4- late onset | .08 | -0.60 | 1.65 | -0.09 |
| Hyperactivity/impulsivity unconditional | | | | |
| 1- persistent | .08 | 1.10 | 0.23 | -0.07 |
| 2- remitting | .13 | 1.33 | -1.69 | -0.07 |
| 3- unaffected | .73 | -0.41 | -0.29 | -0.07 |
| 4- late onset | .05 | -0.53 | 1.74 | -0.07 |
| Inattention conditional on gender | | | | |
| 1- remitting | .10 | 1.122 | -1.302 | -0.17 |
| 2- persistent | .13 | 1.032 | 0.070 | -0.17 |
| 3- late onset | .03 | -0.306 | 1.992 | -0.17 |
| 4- unaffected | .49 | -0.553 | -0.191 | -0.17 |
| 5- mild | .25 | -0.190 | 0.479 | -0.17 |
| Hyperactivity/impulsivity conditional on gender | | | | |
| 1- late onset | .10 | -0.229 | 1.122 | -0.15 |
| 2- persistent | .05 | 1.291 | 0.373 | -0.15 |
| 3- remitting | .15 | 1.232 | -1.391 | -0.15 |
| 4- unaffected | .70 | -0.413 | 0.354 | -0.15 |

Note. *Based on posterior probabilities.

Table 2

Comparison of late adolescent outcomes by trajectory class based on unconditional growth mixture models

| | Outcome mean (SE) by category | | | | Wald test <i>p</i> -value for pairwise tests | | |
|-------------------------------|-------------------------------|--------------|--------------|--------------|--|---------------------------|---------------------------|
| | Persistent | Unaffected | Late onset | Remitting | Late onset vs. Persistent | Late onset vs. Unaffected | Persistent vs. Unaffected |
| Inattention | | | | | | | |
| Prosociality | -0.28 (0.09) | 0.08 (0.04) | -0.16 (0.16) | 0.04 (0.12) | .542 | .154 | <.001 |
| Internalising | -0.33 (0.09) | 0.08 (0.04) | -0.09 (0.13) | 0.37 (0.13) | .157 | .205 | <.001 |
| Proactive/indirect aggression | 0.27 (0.10) | -0.05 (0.04) | 0.31 (0.20) | 0.01 (0.14) | .282 | .009 | <.001 |
| Reactive/physical aggression | 0.39 (0.11) | -0.19 (0.02) | 0.19 (0.11) | -0.19 (0.13) | .856 | .089 | .002 |
| Violent Ideations | 0.49 (0.11) | -0.02 (0.04) | 0.53 (0.24) | -0.04 (0.19) | .909 | .034 | <.001 |
| Delinquency | 1.86 (0.19) | 0.77 (0.03) | 2.36 (0.35) | 0.61 (0.19) | .322 | <.001 | <.001 |
| Cigarette Smoking | 4.28 (0.19) | 3.16 (0.09) | 4.40 (0.30) | 2.68 (0.29) | .736 | <.001 | <.001 |
| Alcohol (beer like) | 2.76 (0.17) | 3.05 (0.07) | 2.93 (0.29) | 2.54 (0.29) | .649 | .686 | .125 |
| Alcohol (spirits) | 2.42 (0.24) | 2.57 (0.07) | 2.83 (0.31) | 2.30 (0.37) | .366 | .426 | .528 |
| ADHD symptoms | 0.05 (0.08) | -0.05 (0.03) | 0.23 (0.15) | 0.07 (0.11) | .318 | .075 | .282 |

| | Hyperactivity/impulsivity | | | | | | |
|-------------------------------|----------------------------------|--------------|--------------|--------------|------|-------|-------|
| Prosociality | -0.10 (0.16) | 0.05 (0.03) | -0.04 (0.11) | -0.24 (0.08) | .816 | .425 | .381 |
| Internalising | -0.42 (0.11) | 0.10 (0.03) | -0.26 (0.11) | -0.04 (0.08) | .360 | .002 | <.001 |
| Proactive/indirect aggression | 0.43 (0.11) | -0.05 (0.03) | 0.21 (0.11) | 0.24 (0.08) | .017 | .074 | <.001 |
| Reactive/physical aggression | 1.12 (0.21) | 0.01 (0.02) | 0.32 (0.17) | 0.36 (0.09) | .184 | .029 | <.001 |
| Violent Ideations | 0.65 (0.15) | -0.00 (0.03) | 0.28 (0.12) | 0.39 (0.10) | .078 | .022 | <.001 |
| Delinquency | 1.62 (0.29) | 0.98 (0.04) | 1.47 (0.22) | 1.24 (0.13) | .732 | .032 | .027 |
| Cigarette Smoking* | 4.17 (0.30) | 3.17 (0.08) | 4.44 (0.25) | 3.72 (0.20) | .503 | <.001 | .002 |
| Alcohol (beer like) | 3.29 (0.29) | 2.92 (0.07) | 2.92 (0.24) | 2.86 (0.17) | .373 | .999 | .211 |
| Alcohol (spirits) | 2.93 (0.26) | 2.51 (0.06) | 2.88 (0.25) | 2.34 (0.15) | .895 | .105 | .105 |
| ADHD symptoms | 0.30 (0.13) | -0.06 (0.03) | 0.03 (0.11) | 0.17 (0.08) | .123 | .440 | .005 |

Table 3

Comparison of late adolescent outcomes by trajectory class based on growth mixture models controlling for gender

| | Outcome means by category | | | | | Wald test <i>p</i> -value | | |
|-------------------------------|---------------------------|--------------|--------------|--------------|--------------|---------------------------|------------|------------|
| | Persistent | Unaffected | Late onset | Remitting | Mild | Late onset | Late onset | Persistent |
| | | | | | | vs. | vs. | vs. |
| | | | | | | Persistent | Unaffected | Unaffected |
| Inattention | | | | | | | | |
| Prosociality | -0.33 (0.11) | 0.11 (0.04) | -0.08 (0.18) | -0.08 (0.12) | -0.07 (0.09) | .27 | .304 | <.001 |
| Internalising | -0.33 (0.09) | 0.11 (0.04) | -0.32 (0.17) | 0.22 (0.12) | -0.05 (0.08) | .96 | .014 | <.001 |
| Proactive/indirect aggression | 0.26 (0.09) | -0.10 (0.04) | 0.50 (0.19) | -0.05 (0.10) | 0.21 (0.08) | .279 | .002 | <.001 |
| Reactive/physical aggression | 0.67 (0.09) | -0.08 (0.03) | 0.97 (0.22) | 0.11 (0.09) | 0.30 (0.07) | .233 | <.001 | <.001 |
| Violent Ideations | 0.44 (0.09) | -0.09 (0.03) | 0.56 (0.19) | 0.05 (0.10) | 0.38 (0.08) | .619 | .001 | <.001 |
| Delinquency | 1.50 (0.15) | 0.89 (0.04) | 1.55 (0.32) | 0.97 (0.15) | 1.34 (0.11) | .897 | .038 | <.001 |

| | | | | | | | | |
|----------------------------------|--------------|--------------|--------------|--------------|-------------|------|-------|-------|
| Cigarette Smoking | 4.09 (0.22) | 2.89 (0.09) | 4.71 (0.42) | 2.98 (0.28) | 4.29 (0.20) | .219 | <.001 | <.001 |
| Alcohol (beer like) | 2.72 (0.19) | 2.97 (0.09) | 2.65 (0.38) | 2.50 (0.21) | 3.27 (0.19) | .887 | .411 | .216 |
| Alcohol (spirits) | 2.52 (0.17) | 2.45 (0.07) | 2.26 (0.36) | 2.17 (0.20) | 2.89 (0.16) | .548 | .517 | .924 |
| ADHD symptoms | 0.10 (0.09) | -0.06 (0.04) | 0.15 (0.16) | 0.00 (0.11) | 0.07 (0.08) | .807 | .213 | .109 |
| Hyperactivity/impulsivity | | | | | | | | |
| Prosociality | -0.14 (0.14) | 0.07 (0.03) | -0.08 (0.11) | -0.29 (0.09) | - | .767 | .186 | .160 |
| Internalising | -0.42 (0.11) | 0.13 (0.03) | -0.31 (0.11) | -0.17 (0.08) | - | .465 | <.001 | <.001 |
| Proactive/indirect aggression | 0.43 (0.11) | -0.06 (0.03) | 0.20 (0.10) | 0.27 (0.08) | - | .140 | .017 | <.001 |
| Reactive/physical aggression | 0.91 (0.10) | -0.00 (0.02) | 0.43 (0.08) | 0.43 (0.08) | - | .002 | <.001 | <.001 |
| Violent Ideations | 0.60 (0.11) | -0.01 (0.03) | 0.31 (0.10) | 0.39 (0.08) | - | .066 | .004 | <.001 |
| Delinquency | 1.59 (0.20) | 0.97 (0.04) | 1.43 (0.16) | 1.29 (0.12) | - | .555 | .005 | .002 |

| | | | | | | | | |
|---------------------|-------------|--------------|-------------|-------------|---|------|-------|------|
| Cigarette Smoking | 4.15 (0.29) | 3.15 (0.08) | 4.46 (0.26) | 3.79 (0.20) | - | .456 | <.001 | .001 |
| Alcohol (beer like) | 3.33 (0.27) | 2.90 (0.07) | 3.00 (0.23) | 2.89 (0.17) | | .387 | .665 | .124 |
| Alcohol (spirits) | 2.96 (0.24) | 2.49 (0.06) | 2.87 (0.21) | 2.37 (0.16) | - | .801 | .084 | .052 |
| ADHD symptoms | 0.30 (0.12) | -0.05 (0.03) | 0.02 (0.11) | 0.13 (0.08) | - | .086 | .532 | .003 |

Figure 1

Unconditional inattention trajectories

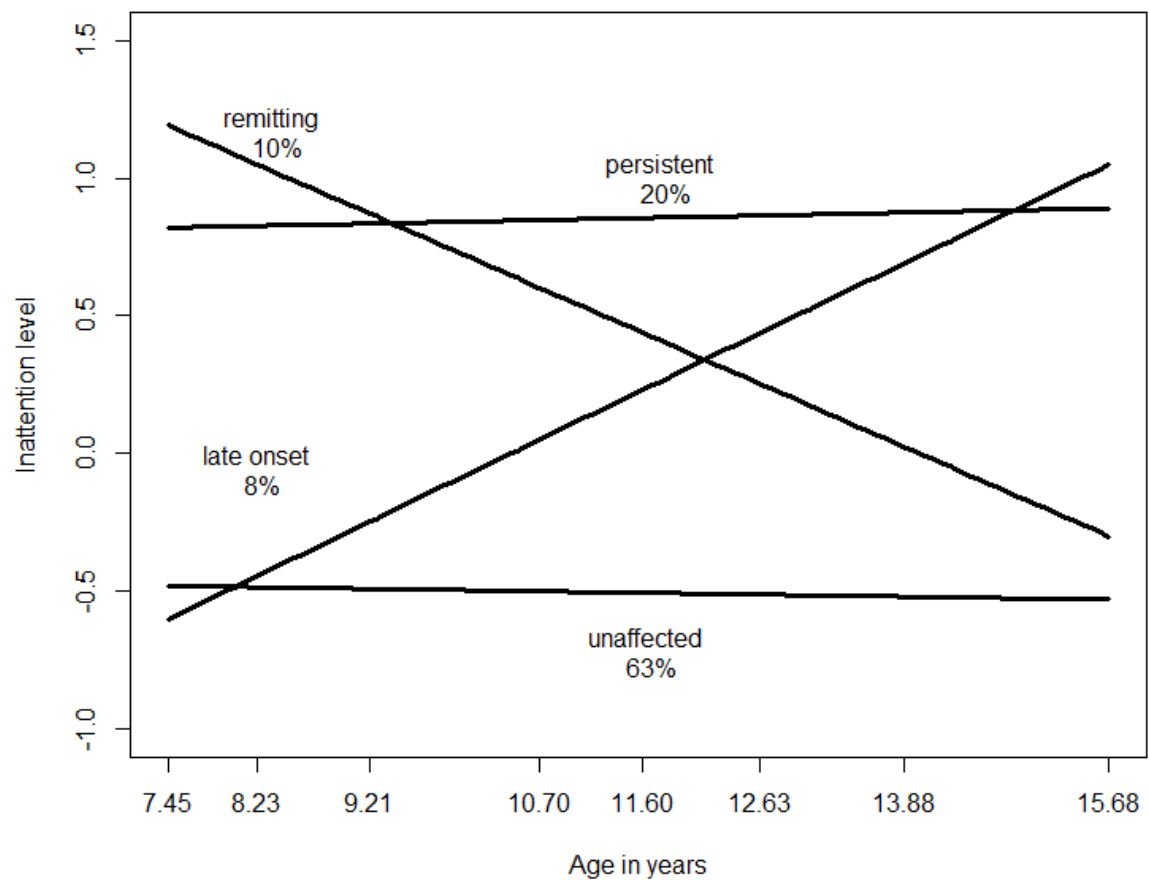


Figure 2

Unconditional hyperactivity/impulsivity trajectories

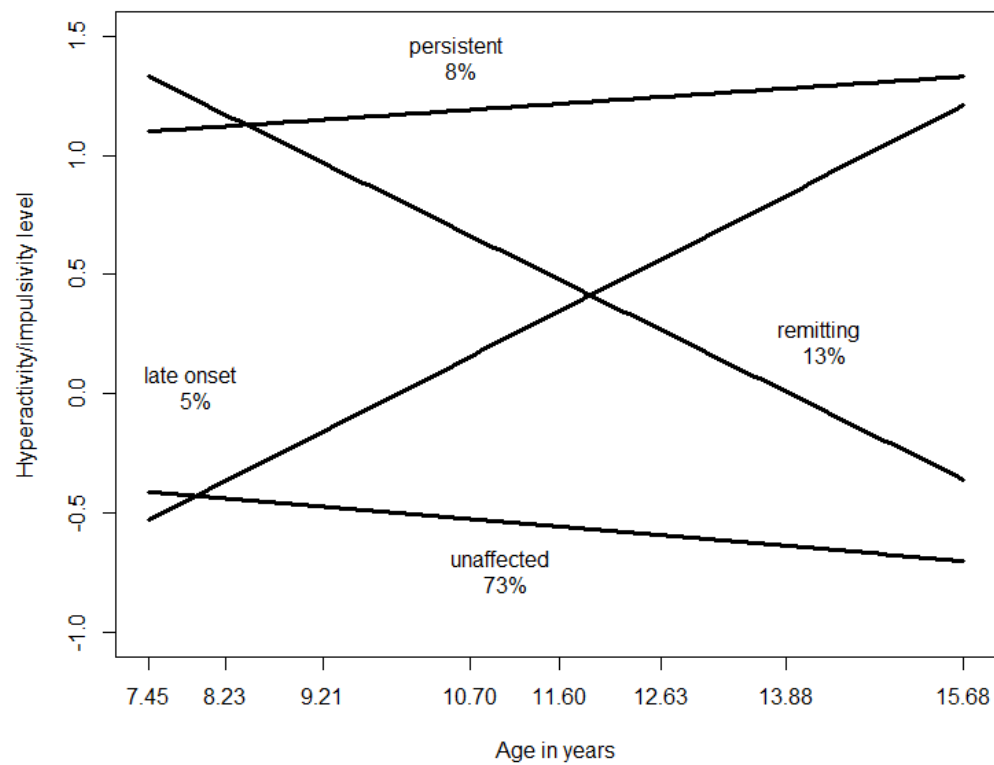


Figure 3

Trajectories for inattention conditional on gender

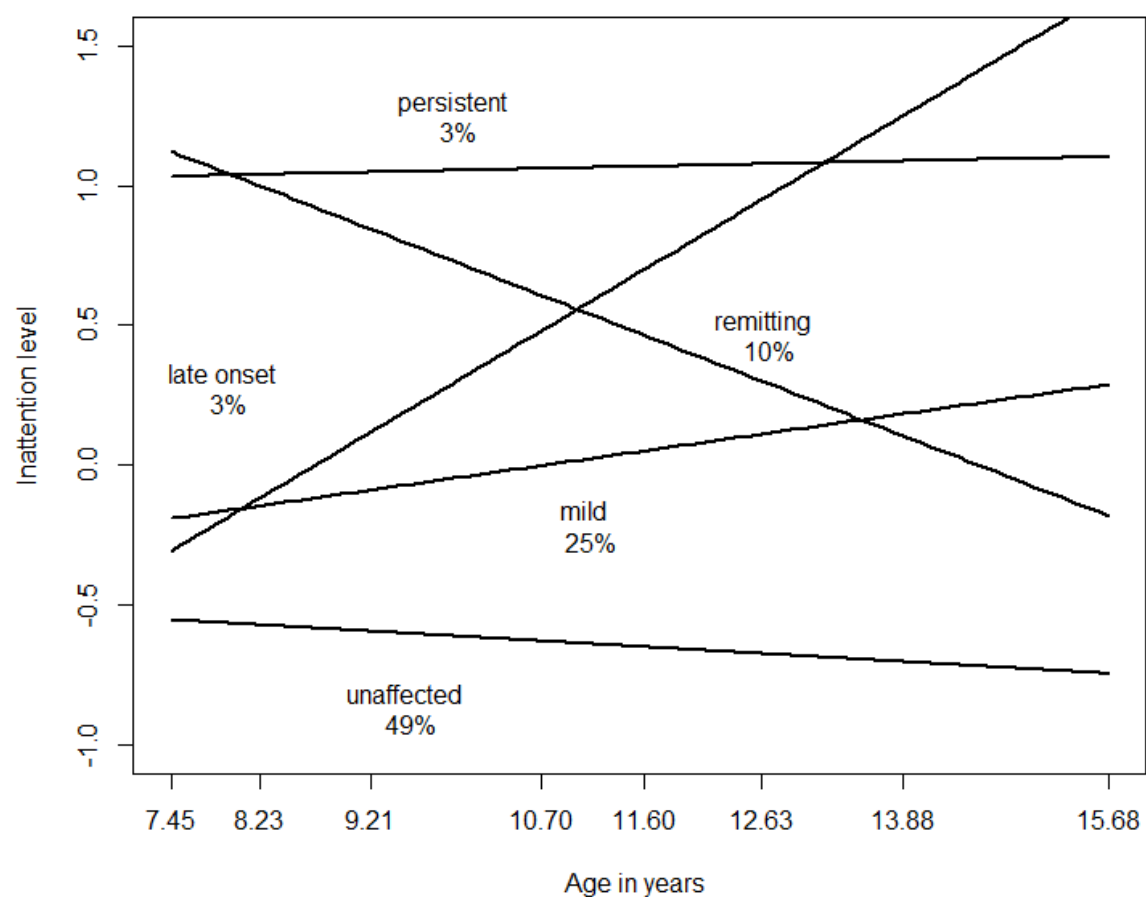


Figure 4

Trajectories for hyperactivity/impulsivity conditional on gender

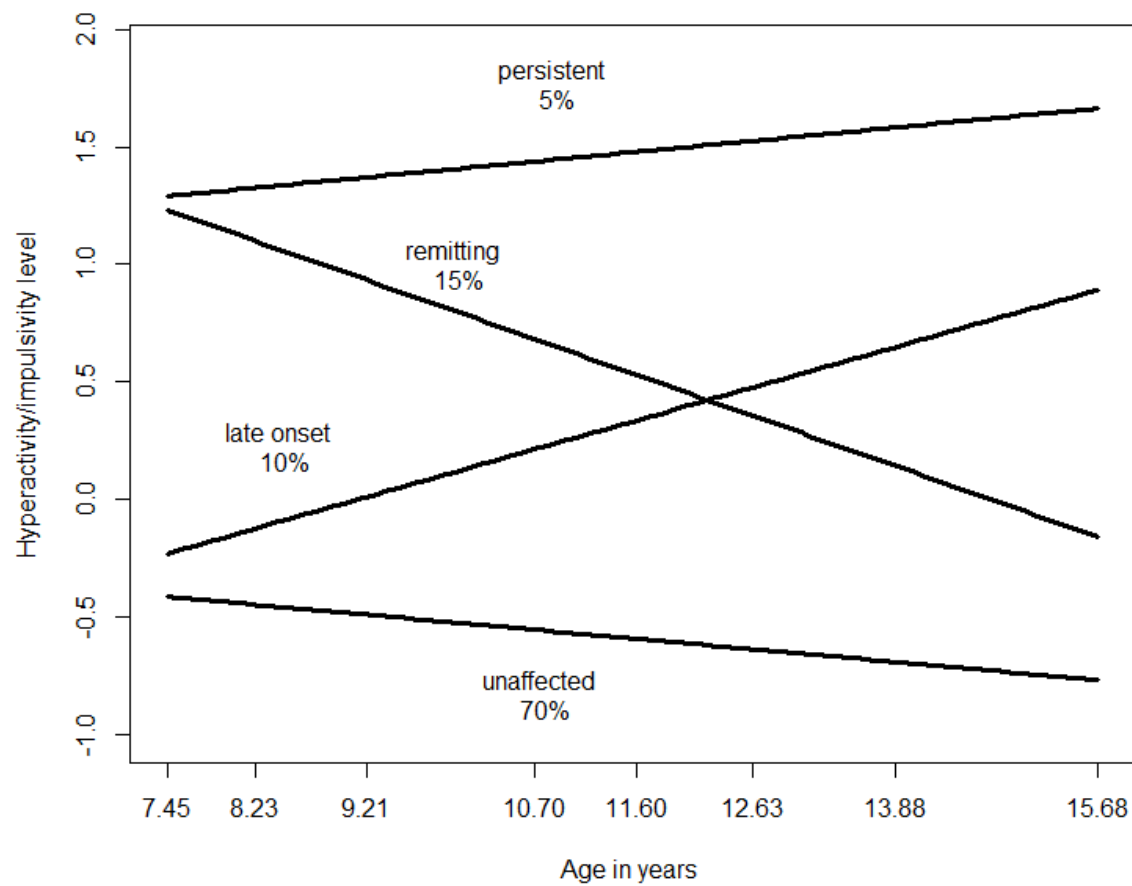


Figure Legends

Figure 1: Inattention trajectory classes from unconditional growth mixture models

Figure 2: Hyperactivity/impulsivity trajectory classes from unconditional growth mixture models

Figure 3: Inattention trajectory classes from growth mixture models conditional on gender

Figure 4: Hyperactivity/impulsivity trajectory classes from growth mixture models conditional on gender